REMARKS

Reconsideration of the present Application in view of the present Amendments and the following remarks is respectfully requested. Claims 21, 22, 24-39, and 41-60 are pending. Applicants acknowledge the Examiner's notation in the Office Action that the Appendix of Currently Pending Claims submitted by Applicants with the Response filed March 4, 2003 did not include claim 31. Applicants submit that omission of claim 31 was an inadvertent error, and the claim is included in the present Listing of the Claims that begins on page 2 of this Response. Applicants have amended claims 41-43 to define more clearly the subject matter encompassed by Applicants' invention. Support for the amended claims may be found in the specification, for example, at page 4, lines 24-34; at page 9, line 32 through page 10, line 7; and at page 17, line 18 through page 18, line 22. No new matter has been added.

REJECTION UNDER 35 U.S.C. § 112, FIRST PARAGRAPH (WRITTEN DESCRIPTION)

The Examiner rejects claims 21-22, 24-37, 41-60 under 35 U.S.C. § 112, first paragraph, alleging that the claims are directed to subject matter that is not adequately described in the specification. The Examiner alleges that the recitation "wherein the first fraction has not been subjected to a method for isolating a cancer cell" constitutes new matter that is not supported by the specification.

Applicants respectfully traverse this rejection and submit that Applicants possessed the claimed invention, as disclosed in the present specification and recited in the instant claims, at the time the Application was filed. Applicants' invention is directed to a method for determining an increased risk for or presence of a disseminated cancer cell or a micrometastasizing cancer cell in a body fluid from a subject, comprising in pertinent part detecting in a plurality of cells obtained from a body fluid of a subject as recited, an absence or presence of at least one first nucleic acid selected from a first cancer-specific nucleic acid or a first cancer-associated nucleic acid, wherein the body fluid has not been subjected to a method for isolating cancer cells from non-cancer cells, and wherein the first cancer-associated nucleic acid is not expressed in the non-cancer cells.

Applicants submit that when the specification is considered as a whole, a person skilled in the art would understand that the invention relates to at least two nucleic acid detection

steps: one step being detection of a (first) nucleic acid in a sample which has not specifically been enriched for cancer cells, and the other step being detection of a (second) nucleic acid in a sample that has been enriched for cancer cells. Applicants therefore respectfully submit that the phrase "wherein the body fluid has not been subjected to a method for isolating cancer cells from non-cancer cells" recited in step (a) of claims 41-43 (upon which claims 21-22, 24-37, 44-60 ultimately depend) does not introduce new matter.

The specification describes one step as investigation of a sample that has not been enriched for cancer cells by teaching that a plurality of cells obtained from a body fluid of an individual are investigated for at least one cancer-specific and/or cancer-associated nucleic acid (*see, e.g.,* page 4, lines 27-29, "cells obtained from body fluid from an individual are investigated"; page 9, line 31 through page 10, line 7), and that this plurality of cells may be obtained from a cell-containing concentrate of the body fluid or a cell-containing liquid from the body fluid (*see, e.g.,* page 17, lines 19-23). The specification also explicitly describes that in another, distinct step of the claimed method, the body fluid from the individual is subjected to a method for isolation of cancer cells (*see, e.g.,* page 4, lines 29-34, "*and* cancer cells removed from body fluid from an individual are investigated" (emphasis added); page 10, lines 3-7; page 17, line 34 through page 18, line 22). These isolated cancer cells are analyzed for the presence of a second cancer-specific nucleic acid and/or a second cancer-associated nucleic acid and compared with the presence of the same cancer-specific and/or cancer-associated nucleic acid in a non-cancer cell obtained from the body fluid of the same subject (*see, e.g.,* page 4, lines 24-34; page 17, line 18 through page 19, line 8).

Wherever the specification describes investigation of isolated cancer cells, and as is readily apparent from the above-noted citations, the passage is immediately preceded by a description of analyzing a plurality of cells from a body fluid without any description of removing cancer cells (*see also* originally filed claims 1 and 2). Thus, one skilled in the art would readily ascertain that the specification describes a method for determining an increased risk for or presence of a disseminated cancer cell or micrometastasizing cancer cell that comprises analyzing a plurality of cells from a body fluid for the presence or absence of a first nucleic acid as recited, wherein the plurality of cells is *not* subjected to a method for removal of cancer cells. In *another, distinct* step (*e.g.,* page 4, lines 29-34, "*and* cancer cells removed from

body fluid from an individual are investigated" (emphasis added)), the body fluid is subjected to a method for removing cancer cells, thus enriching for cancer cells, followed by investigation for the presence or absence of a second nucleic acid as recited.

Furthermore, and contrary to the assertion by the Examiner, while the specification discloses in separate examples the procedures describing the isolation of fraction A that is not enriched for cancer cells and the isolation of tumor cells in fraction C, the specification nonetheless specifically describes and exemplifies methods for identification and characterization of disseminated and micrometastasized cancer cells in both fraction A and fraction C (*see* Examples 1-8). For instance, as described in any one of Examples 1-8, patients' blood was analyzed for CK20 mRNA and CEA mRNA. As described in Reference Example 4, the presence of these mRNAs was determined with a sensitivity of more than one cell per 10^6 lymphocytes, thus indicating that the determination was carried out in fraction A containing mononuclear cells (MNC) as prepared in Reference Example 1 (*see* page 31, lines 15, 33, and 34 and page 33, line 19). Moreover, the specification expressly describes that this method may be performed without previous removal of the cancer cells and that the MNC fraction is preferably used in blood investigations (*see, e.g.*, page 21, lines 34-36). The specification thus unambiguously conveys to a person skilled in the art that the MNC fraction has not been subjected to a method for isolating cancer cells from non-cancer cells. The specification also describes that the claimed method comprises the additional analysis of nucleic acids from a cell fraction in which cancer cells are enriched (*see* Examples 1-8). For example, the amplification of erb-B2 and c-myc was performed after tumor cell isolation (*see, e.g.*, Examples 1, 5-8; *see also, e.g.*, Example 10: loss of heterozygosity analyses performed using fraction A and fraction C (page 45, lines 11-19)).

Accordingly, Applicants respectfully submit that the amendments to the claims do not introduce new matter and thus meet the written description requirement under 35 U.S.C. § 112, first paragraph. Applicants respectfully request that the rejection of these claims be withdrawn.

REJECTIONS UNDER 35 U.S.C. § 103

Claims 21-22, 24-28, 32, 36-37, 41-45, 49-51, 54-59 stand rejected under 35 U.S.C. § 103. The Examiner asserts the claims are obvious over Jung et al. (*Eur. J. Clin. Chem. Clin. Biochem.* 35:3-10 (1997)) and Rimm et al. (U.S. Pat. No. 6,197,523 (March, 2001)) or Ts'o et al. (U.S. Pat. No. 5,962,237 (October, 1999)) in view of Hoon et al. (U.S. Pat. No. 6,057,105 (May, 2000)). This rejection is based upon the interpretation that the claims encompass detection of a nucleic acid in both an enriched sample and in a sample that has not been enriched for cancer cells. More specifically, the Examiner alleges that a person having ordinary skill in the art would have been motivated to combine the teachings of Jung et al. (detection of single metastatic cancer cells by RT-PCR in a peripheral blood sample) and Rimm et al. (performing two different types of assays using the same cell sample) or Ts'o et al. (removing non-rare cells from a fluid to increase the number of cancer cells in a sample) in view of Hoon et al., who disclose a method for detecting metastasis of melanoma and breast cancer using more than one cancer cell marker, to obtain Applicants' invention.

Applicants respectfully traverse these grounds for rejection and submit that the claimed methods would not have been obvious to persons having ordinary skill in the art at the time the application was filed. Applicants' invention is directed in pertinent part to a method for determining an increased risk for or presence of a disseminated cancer cell or a micrometastasizing cancer cell in a body fluid from a subject, comprising the following features: (i) detecting a first nucleic acid in unfractionated body fluid cells, the first nucleic acid being a cancer-specific nucleic acid (which is by definition not expressed in non-cancer cells, *e.g.*, specification at pg. 5, lines 31-34) or a cancer-associated nucleic acid (that is not expressed in the non-cancer cell of the body fluid investigated, *see, e.g.*, page 9, line 32 through page 10, line 7) (step (a) of claims 41-43), and (ii) detecting a second nucleic acid in both of an isolated cancer cell (step (c) of claims 41-43) *and* in a non-cancer cell (step (d) of claims 41-42 and step (e) of claim 43), wherein (iii) the second nucleic acid is different from the first nucleic acid.

Applicants submit that a person having ordinary skill in the art would not have been motivated by the prior art, including the references cited in the Action, to arrive at the present invention with any reasonable expectation of success. Accordingly, and for reasons discussed herein, applicants respectfully submit that the Examiner has not established a *prima*

facie case of obviousness. (*See In re Mayne*, 104 F.3d 133, 1341-43, 41 U.S.P.Q.2d 1451 (Fed. Cir. 1997) (PTO has the burden of showing a *prima facie* case of obviousness.)). The Examiner must show (1) that the combined references teach or suggest all claim limitations; (2) that the references provide some teaching, suggestion, or motivation to combine or modify the teachings of the prior art to produce the claimed invention; and (3) that the combined teachings of the references indicate that by combining the references, a person having ordinary skill in the art will achieve the claimed invention with a reasonable expectation of success. When rejection of claims depends upon a combination of prior art references, a teaching, motivation, or suggestion to combine the references must exist. (*See In re Rouffet*, 149 F.3d 1350, 1355, 47 U.S.P.Q.2d 1453 (Fed. Cir. 1998)).

The cited documents, alone or in combination, fail to teach or suggest the presently claimed method. In particular, the combination of cited references fails in any way to suggest a method comprising (a) detecting a first nucleic acid in unfractionated body fluid cells, the first nucleic acid being a cancer-specific nucleic acid or a cancer-associated nucleic acid; (b) detecting a second nucleic acid in both of an isolated cancer cell and a non-cancer cell; wherein the first nucleic acid is different from the second nucleic acid.

Jung et al. teach a RT-PCR method for detecting a single polynucleotide encoding a tumor related antigen solely in an unfractionated sample such as peripheral blood. For reasons already made of record, Jung et al. fail to teach or suggest detecting a first nucleic acid in a plurality of cells from a body fluid and detecting a second nucleic acid in a cell fraction that has been enriched for cancer cells. Moreover, Jung et al. suggest that "no enrichment of nucleated cells [including cancer cells] is necessary," thus teaching away from the claimed method comprising detecting cancer-specific or cancer-associated nucleic acids in both an enriched and an unenriched fraction of cells from a body fluid. Instead, Jung et al. suggest that to improve sensitivity, improvements to test standardization and internal quality control should be made, which requires a higher grade of automation, processing of larger samples, and increase in efficiency of reverse transcription (*see* Jung et al. at page 9).

Rimm et al. (Rimm) teach a method for visually or photometrically detecting circulating cancer and/or hematologic progenitor cells in an anticoagulated whole blood sample. The method is purported to rely on the observation that circulating cancer cells that are of

epithelial origin, when present in the circulating blood stream, have a different density than other nucleated constituents of blood (Rimm, column 4, lines 4-7). Rimm suggests that the method is useful for distinguishing between malignant and benign cells of epithelial origin (column 4, lines 26-28). Accordingly, one step of the method involves detection of epithelial-specific antigens to determine the epithelial origin, which step is referred to as the epitopic step (see column 4, lines 45-55). Another step involves the morphological examination of the cells (column 5, lines 3-9). Rimm notes in column 2, lines 50-52, that visual morphological analysis of cells is the most reliable way to distinguish cancerous epithelial cells from benign epithelial cells.

According to Rimm, the benefit of the method disclosed therein is that both the epitopic and morphometric analyses may be performed *in situ*, that is, in a closed sampling system. In contrast to the teachings of Jung and Hoon discussed herein, Rimm teaches that molecular and immunophenotypic methods such as reverse transcription in conjunction with polymerase chain reaction and fluorescent activated cell sorting are disadvantageous methods that do not use *in situ* cytopathologically-based analyses to determine the morphometric characteristics of circulating cancer cells (*see* Rimm, column 1, line 65 to column 2, line 38).

Therefore, the objective teaching of Rimm is directed to the determination of morphometric and epitopical characteristics of circulating cancer cells in a sample that has been enriched for cancer cells. This method does not rely upon nucleic acid detection. As described in Rimm, circulating nucleated cells are identified by cell morphology, and all identified nucleated cells that by reason of their morphology may be cancer cells are further characterized as cancer or non-cancer cells epitopically (column 14, lines 13-17). Nucleic acid analysis, however, is mentioned as an optional means only for verifying the results obtained by the morphometric analyses (column 12, lines 1-11). Furthermore, one skilled in the art would derive from Rimm that nucleic acid analysis is <u>not</u> desirable because detecting the absence or presence of nucleic acid requires removing cells from the closed sampling system, and thus the alleged benefit of the *in situ* analysis according to Rimm would be lost (*see* column 12, lines 1-11).

Rimm also fails to teach or suggest that the same nucleic acid analysis is performed with non-cancer cells from the subject under investigation, which in addition to cancer cells, would require removing non-cancer cells from Rimm's sampling tube. Rimm further fails to teach or suggest that nucleic acids are detected in a sample that is not enriched for

cancer cells; Rimm only discusses analysis of a sample that is enriched for cancer cells. Applicants further submit that Rimm, if anything, teaches away from the present invention. A person having ordinary skill in the art would not find it obvious to use the optional embodiments taught by Rimm in combination with any of the other cited documents to obtain Applicants' invention, particularly when, according to Rimm, doing so would be a disadvantage and not beneficial.

Ts'o et al. (Ts'o) describe a method for enriching cancer cells from a fluid that comprises cancer cells and non-cancer cells, and in which processing of enriched cancer cells may include detection of specific nucleic acids (column 2, lines 45-51). Ts'o also teaches that cancer cells are heterogeneous in nature and that certain kinds of cancer cells can have densities that are similar to that of nucleated white blood cells; thus, the described method requires performing density gradient separation at least twice (column 6, lines 16-24). In addition, Ts'o distinguishes between lighter cancer cells and relatively heavier cancer cells that are found in different locations in the density gradient (column 6, lines 44-51). Thus, Ts'o describes two fractions that both comprise an increased concentration of cancer cells, that is, both fractions are enriched for cancer cells, each of which can be analyzed by methods for detecting nucleic acids. However, Ts'o fails to teach or suggest that the same analysis may be carried out with non-cancer cells from the subject under investigation. Even if, for the sake of argument, one nucleic acid that is detected according to the method of Ts'o was only expressed in cancer cells and would not therefore require prior cancer cell enrichment, Ts'o nevertheless fails to teach or suggest that a nucleic acid detected in one fraction is different than the nucleic acid detected in the second fraction. On the contrary, Ts'o teaches that the two fractions are recombined and then analyzed further (*see* Ts'o, claim 1). Therefore, if anything, Ts'o teaches away from detecting different nucleic acids in separate fractions.

Contrary to the assertion by the Action, Hoon et al. (Hoon) fail to provide the requisite suggestion or teaching for combining the teachings of any of the cited documents to achieve Applicants' invention. Hoon teaches a method for detecting one or more markers of a melanoma or breast cancer cell in cells from a subject having cancer, and detecting the presence of the same markers in cells from persons who do not have the disease or in biopsies of tissues different from the tissues originally tested. Hoon fails, however, to teach or suggest detecting the

presence or absence of a marker in a cancer cell and a non-cancer cell, each isolated from a body fluid of the same subject.

Furthermore, in contradistinction to the feature of the present invention whereby the second nucleic acid is detected in both cancer and non-cancer cells from the same subject, Hoon clearly states that if a candidate marker is detectable in normal cells, it is *not* a reliable marker for detecting circulating cancer cells. For instance, Example X of Hoon describes that peripheral blood lymphocytes (PBL) from normal volunteer donors expressed β-HCG/LH receptor mRNA indicating that this receptor is not a reliable marker for detecting breast cancer cells in blood or lymph nodes (column 28, lines 25-36). By contrast, as described in the present specification, cancer-associated genes include those that are expressed in healthy cells or in a wide variety of other disorders, but may be characteristically modulated in cancer cells in comparison with non-cancer cells, such that conclusions may be drawn about the nature and the behavior of the cancer cells (*see, e.g.,* page 5, line 30 through page 6, line 23).

Furthermore, Hoon particularly fails to teach or suggest detecting a nucleic acid in an isolated cancer cell *and* a non-cancer cell from the *same* subject known to have or suspected of being at risk for having a disseminated cancer cell or a micrometastasized cancer cell. While Hoon refers to analyses of normal cells (*see, e.g.,* Example III, column 18, line 40; Example IX, column 26, lines 56-57; Example X, column 28, lines 31-32; Example XIV, column 33, lines 34-36; column 34, lines 20-21, column 35, lines 27-28; Example XVI, column 40, line 55; column 43, lines 42, 50), the samples were derived either from individuals known to be healthy or from tissues from other cancer patients, which tissues were known to be negative for tumor cells. The samples served to ascertain whether a candidate marker gene was essentially not expressed in healthy individuals and/or normal tissues, and therefore Hoon taught that the marker can be a reliable tumor marker. Thus, the evaluation of the normal samples relates to proof of principle and not to assessment of a particular patient.

Applicants submit that the cited publications fail to provide the requisite *desirability* of combining the cited disclosures to obtain the claimed polynucleotides. *See In re Fritch*, 922 F.2d 1260, 23 U.S.P.Q.2d 1780 (Fed. Cir. 1992) (The mere fact that modification of the prior art *may* reflect features of the claimed invention does not make the invention obvious unless desirability of the modification is suggested by the prior art.) (Emphasis added).

Applicants further submit that each of the cited documents suggests that the respective methods disclosed therein for detecting the presence of cancer cells are sufficient and, with the exception of Jung as discussed above, do not teach or suggest that additional sensitivity is desired or required. Moreover, none of the documents teach or suggest, alone or in combination, detecting a first nucleic acid in a body fluid from a subject that is not enriched for cancer cells *and* detecting a *second different* nucleic acid in a *second* sample that is enriched for cancer cells, *and* detecting this same second different nucleic acid in non-cancer cells from the same subject.

At best, the PTO's assertion of nonobviousness relies on the illegitimate test that an ordinarily skilled artisan might find it "obvious to try" to obtain the claimed methods using the disclosure of any of the cited documents. *See In re Fine*, 837 F.2d 1071, 1075 (Fed. Cir. 1988) ("...[W]hether a particular combination might be "obvious to try" is not a legitimate test of patentability."). However, the skilled artisan could not have reasonably expected to obtain the claimed subject matter because the cited documents provide no guidance for obtaining the claimed method with the recited steps.

The present invention addresses the problem that circulating cancer cells are notoriously heterogenous. When cancer cells detach from the primary tumor, their molecular profile is quite similar to that of the cells of the primary tumor. For instance, the cells express epithelial markers that allow Rimm to perform an epitopic analysis to confirm their epithelial origin and that allow Schmitz to isolate the cells by immunomagnetic adsorption techniques (see below). However, over a time interval, the disseminated cancer cells proliferate and some undergo transitions that alter their molecular profile. In particular, these transitions may involve the loss of certain antigens, induction of angiogenesis, resistance against growth inhibiting signals, loss of cell to cell coupling, resistance against apoptosis, immortalization, and primary resistance against cytoreductive therapies, and changes in cell size (*see also, e.g.*, specification, page 24, line 9 through page 27, line 33). All the cited documents fail to appreciate that differences in the molecular profile of cells indicate a different impact on the patient's risk for developing metastases. The claimed methods accurately determine the risk that a subject may develop or has developed metastases by analyzing the presence of a first cancer-specific or cancer-associated nucleic acid in cells that have not been subjected to a method for isolating

cancer cells, in combination with analysis of isolated cancer cells to detect a second cancer-specific or cancer-associated nucleic acid.

The present specification teaches the unexpected benefits of the claimed methods in the examples. For instance, the patient described in Example 5 had a breast carcinoma. Following the teachings of Hoon and Jung, a person skilled in the art would have determined the presence of mRNAs, such as CK20, CEA, and MUC1, in the MNC fraction. The results presented in Example 5 showed that all three markers were detected. Taking this result alone, a person skilled in the art would have concluded that the patient was at high risk of developing metastases. According to the claimed method, however, the analysis of the cancer cell fractions indicated the lack of genomic imbalances (*e.g.*, p53 mutation; amplifications of erb-B2 and c-myc); therefore, the risk of developing metastases was rather low (and which is also confirmed by the absence of metastasis-associated mRNAs). This profile is in contrast to that of the patient described in Example 1 in which not only were the three epithelial markers (CK20, CEA, and MUC1) found to be positive, but the isolated cancer cells were detected as having two genomic imbalances (amplifications of erb-B2 and c-myc). Thus the risk for this patient to develop metastases was determined to be rather high (poor prognosis), which was corroborated by the presence of several metastasis-associated mRNAs. Similar results were obtained for the patients described in Examples 2, 3, and 4.

Applicants therefore respectfully submit that the subject matter of the claims is nonobvious as required under 35 U.S.C. § 103 and respectfully request that the rejection of the claims be withdrawn.

The Examiner rejects claims 29-31, 33-35, 46-48 under 35 U.S.C. § 103, asserting obviousness over Jung et al. (*Eur. J. Clin. Chem. Clin. Biochem.* 35:3-10 (1997)) and Rimm et al. (U.S. Pat. No. 6,197,523 (March, 2001)) or Ts'o et al. (U.S. Pat. No. 5,962,237 (October, 1999)) further in view of Hoon et al. (U.S. Pat. No. 6,057,105 (May, 2000)), and further in view of Schmitz et al. (U.S. Pat. No. 6,190,870 (February 2001), Popescu et al. (*Cancer Gen. Cytogenet.* 93:10-21(1997), or Torczynski it al. (U.S. Pat No. 5,589,579 (December 1996), and further in view of Hoon et al. (U.S. Pat. 6,057,105 (May 2, 2000)). The Examiner concedes that none of Jung et al., Rimm et al., Ts'o et al., or Hoon et al. specifically teaches the analysis of

oncogenes, tumor suppressor genes, or other specifically recited genes. However, the Examiner asserts that Schmitz et al. teach that tumor cells may be separated from peripheral blood by magnetic sorting, using any one of several separation markers that may be present on the cell surface or within the cytoplasm of tumor cells. The Examiner further asserts that at the time the instant application was filed, a person having ordinary skill in the art would have found it obvious to combine the teachings of Schmitz et al. to modify the method of Jung, Rimm, Ts'o in view of Hoon to obtain a method using any combination of markers depending upon the suspected form of cancer, or using a combination that is more applicable to cancers generically.

Applicants respectfully traverse the basis for this rejection and submit that the documents cited by the Action, alone or in combination, fail to teach or suggest the subject matter of the instant claims. As conceded by the Action, Jung, Rimm, Ts'o, and Hoon all fail to teach the analysis of oncogenes, tumor suppressor genes, or other specifically recited genes. For reasons discussed above with respect to the documents cited in the preceding rejection, each of Schmitz et al., Popescu et al., and Torczynski et al., also fails to teach or suggest a method for determining an increased risk for or presence of a disseminated cancer cell or a micrometastasizing cancer cell, comprising detecting a first cancer-specific or cancer-associated nucleic acid in a plurality of cells that has not been subjected to a method for isolating cancer cells from non-cancer cells and detecting a second cancer-specific or cancer-associated nucleic acid in a second fraction that has been subjected to such a method. Each of the cited publications also fails to teach or suggest that the at least one first cancer-specific or cancer-associated nucleic acid detected in the plurality of cells is different from the at least one second cancer-specific or cancer-associated nucleic acid in the cancer cell enriched fraction. Also, none of the cited documents teaches or suggests detecting the second nucleic acid in a non-cancer cell from the subject.

For reasons already made of record, Schmitz et al. teach a method for enriching carcinoma cells and analyzing only the enriched fraction to quantify the number of cancer cells present in the sample. Applicants submit that Popescu et al., Torczynski et al., and Hoon et al. all fail to remedy the deficiencies of Schmitz et al. Popescu et al., merely provide a general review of several cytogenetic methods, including FISH, for detecting chromosomal abnormalities in cancer cells. Popescu et al. fail to suggest any desirability of using FISH for

analyzing unfractionated cells and a fraction enriched for cancer cells, or for analyzing disseminated or micrometastasized cells. Torczynski et al. disclose a method for diagnosing lung cancer using several markers, including those well known in the art such as CEA, NCA, and the ras and myc families of oncogenes. Torczynski et al. fail, however, to suggest any desirability of combining detection of these markers with carcinoma cells enriched according to Schmitz et al., or with any other method known in the art to achieve Applicants' invention. As discussed above, Hoon et al. teach a method for detecting, in cells from a subject, one or more markers of a melanoma or breast cancer cell. Hoon et al. fail to teach or suggest detecting the markers in a first unfractionated sample of a body fluid and in a second fraction enriched for cancer cells. Hoon et al. also fail to teach or suggest detecting the melanoma or breast cancer cell markers in a non-cancer cell isolated from the same subject.

Applicants submit that any combination of Jung, Rimm, Ts'o, Schmitz et al., Popescu et al., Torczynski et al., and Hoon et al. fails to teach or suggest all limitations of Applicants' invention, particularly detection of cancer-specific or cancer-associated nucleic acids in both fractionated and unfractionated cells from a body fluid. Furthermore, none of the cited documents teaches or suggests the requisite modifications of any of the disclosed techniques that would be required to achieve the claimed method; nor do any of the cited documents teach or suggest the desirability of making such modifications. Applicants submit that to so modify the art could only be accomplished using impermissible hindsight in view of the instant application. Applicants therefore submit that the claimed invention is nonobvious as required under 35 U.S.C. § 103 and respectfully request that the rejection of the claims be withdrawn.

Claims 38-39 and 52-53 under 35 U.S.C. § 103 stand rejected for allegedly being obvious over Mitsuhashi (U.S. Patent No. 5,976,797 (November 1999)) in view of Jung et al. and Rimm et al. or T'so et al. in view of Hoon et al., as applied above in the first basis for rejection. The Examiner concedes that none of Jung et al., Rimm et al., Ts'o et al., or Hoon et al. teaches analysis or identification of an anticancer therapy by administering a therapy to samples and detecting presence or expression of markers before and after such administration. The Examiner, however, alleges that an ordinarily skilled artisan would have found it obvious to modify the method of Mitsuhashi for detecting cytotoxic effects of an anticancer compound by

detecting multiple markers in enriched and unenriched cultures. The Examiner further alleges that an ordinary artisan would have been motivated to analyze more than one mRNA for reasons of specificity and reliability as provided by Hoon et al.

Applicants respectfully traverse these grounds for rejection and submit that the subject matter of claims 38-39 and 52-53 is nonobvious. Applicants submit that Mitsuhashi alone or in combination with Jung, Rimm, Ts'o, or Hoon fail to teach or suggest teach or suggest all the limitations of the claimed invention and further submit that none of these documents alone or in combination would have motivated a person having ordinary skill in the art to obtain Applicants' invention with a reasonable expectation of success. As the PTO concedes, Jung et al., Rimm et al., Ts'o et al., and Hoon et al. all fail to teach or suggest analyzing an anticancer therapy or identifying an anticancer therapy by detecting the presence of first and second nucleic acids before and after contacting a candidate anticancer agent with cells.

Mitsuhashi discloses a method for detecting the level of *total* mRNA isolated from cells before and after the cells are exposed to a cytotoxic agent. Mitsuhashi also teaches that the level of a specific mRNA may be measured and compared with the total mRNA from the cells. Mitsuhashi is silent, however, with respect to which *specific* mRNA might be measured and further fails to teach or suggest detecting at least one first cancer-specific or cancer-associated nucleic acid in a plurality of unfractionated cells; Mitsuhashi fails to teach or suggest detecting a second cancer-specific or cancer-associated nucleic acid in a fraction enriched for cancer cells. Mitsuhashi also fails to teach or suggest detecting a cancer-related nucleic acid in non-cancer cells from a biological sample.

For reasons already made of record and as discussed in detail above, Jung, Rimm, Ts'o, and Hoon all fail to teach or suggest detecting one or more cancer-related nucleic acids in both a fractionated and an unfractionated sample. Furthermore, all the cited publications fail to teach or suggest detecting the cancer-related nucleic acid in a non-cancer cell. Applicants submit that Mitsuhashi does not teach or suggest the desirability of combining the method disclosed therein for identifying cytotoxic agents with any other method in the art for detecting disseminated or micrometastasized cells in an unfractionated sample and with any other method for detecting disseminated or micrometastasized cells in a sample enriched for cancer cells. Applicants further submit that none of the cited documents provides any motivation or

suggestion of the desirability of combining the teachings therein and then making the requisite modifications to the disclosures to achieve Applicants' invention.

Applicants respectfully submit that a *prima facie* case of obviousness has not been set forth by the PTO, and submit that Applicants' invention is nonobvious as required under 35 U.S.C. § 103. Applicants therefore request that the rejection of the claims be withdrawn.

Applicants respectfully submit that all claims remaining in the application are allowable. Favorable consideration and a Notice of Allowance are earnestly solicited. In the event that the Examiner believes a teleconference will facilitate prosecution of this case, the Examiner is invited to telephone the undersigned at 206-622-4900.

Respectfully submitted,
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